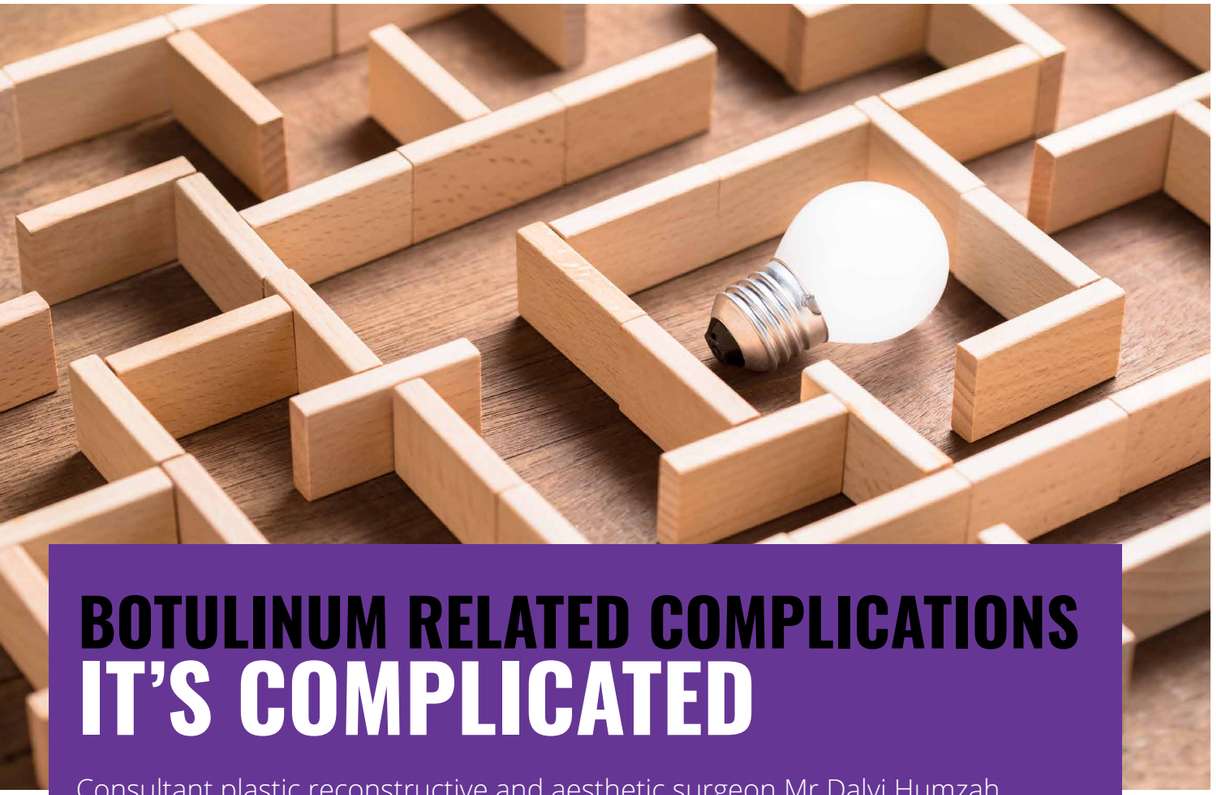

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BOTULINUM RELATED COMPLICATIONS IT'S COMPLICATED

Consultant plastic reconstructive and aesthetic surgeon Mr Dalvi Humzah

Botulinum-related complications are fortunately relatively uncommon and mostly temporary, however, they can cause significant problems to both the patient and practitioner. When considering complications, it is worth thinking about them in relation to the following categories:

- Prevention
- Recognition/treatment
- Recording/reporting

In the following article, we will consider some of these points and, in particular, those complications relating to the use of botulinum toxin in the treatment of upper facial lines in clinical aesthetic procedures.

Some general concepts and issues are helpful to consider. Good planning and techniques with respect to the patient's underlying anatomy reduce the risk of unwanted effects as the accuracy of injection will limit the activity of botulinum toxin to the target muscle(s).

Recent studies on dose-effect relationships appear to show that increased doses in the glabellar region do not result in any increased complications. However, a non-linear increase in longevity is observed as long as the volume of injectate is not increased. A recent study comparing 20 Units of Incobotulinum toxin with 100U in the glabellar did not show any increase in adverse events but did show an increase in longevity of action, similar longevity with increased doses has been demonstrated with Onabotulinum and Abobotulinum toxin[1].

Most complications, as stated previously, are temporary, e.g. temporary muscle weakness, and may be treatable (e.g. eyelid ptosis – discussed later), and most are minor injection-related adverse events, such as erythema bruising or bleeding. Notably, serious complications are rare.

PREVENTION

History: A precise clinical history is mandatory before administering a prescription-only medicine such as botulinum toxin. In particular, a history of drugs that cause bleeding (Aspirin/Clopidogrel) may be implicated in post-injection bleeding and bruising. Other natural "antithrombotics" should also be considered relevant. Excessive use of fish oil may also aggravate bleeding. There are known interactions with muscle relaxants and specific antibiotics. An exhaustive list of these interactions is available on the NICE BNF site[2] (https://bnf.nice.org.uk/interaction/botulinum-toxin-type-a-2.html).

Specific medical neuromuscular conditions, e.g. myasthenia gravis and amyotrophic lateral sclerosis, are uncommon but significantly important conditions that should be sought in the clinical history.

Aseptic technique: All procedures that involve an injection deep to the skin should be approached with adherence to aseptic techniques. Skin cleansing with an appropriate antiseptic and aseptic non-touch techniques should be practised to avoid minor injection site infections.

Injection techniques: Considering the depth and site of injection is imperative in the placement of the toxin intramuscular, subcutaneous and or intradermal depending on the requirement of the treatment administered. In doing so, the spread of the toxin may have adverse effects on other nearby muscles. Therefore, understanding the relationship between topographical and underlying anatomy is necessary to ensure accurate placement.

Injection-related pain is often related to the needle gauge. It is possible to use a gauge of 32G or more to make the injections more comfortable and reduce bleeding from the injection site. A slow injection speed also reduces the perceived pain; intradermal injects also cause more discomfort than intramuscular or subcutaneous injections.

Recognition and treatment
Recognition of complications can be considered in these following timelines:

- Immediate – Mostly allergic
- Early – Mostly injection-related and effects on muscles
- Late – Mostly immunological (resistance)
- Distant – Complications reported in post-marketing reports.

Immediate reactions: These tend to occur within hours of injection. These are relatively rare; the reactions are thought to be related to the excipients included in the toxin preparation, e.g. Human Serum Albumin (HSA). This is purported to be involved in the causation of a rare condition – serum sickness. This is characterised by difficulty in breathing, hives and oedema. There may be difficulty in swallowing related to swelling of the face, lips, mouth or throat. Systemically, this may be related to peripheral oedema. Of interest will be the introduction of new toxins into the market that do not contain excipients like HSA. These reactions are very rare. However, these are issues that need to be considered. For the clinician, it is important to be up to date with current anaphylaxis guidelines, and it is necessary to have the appropriate emergency kit available or a route of referral.

Early: These tend to be non-specific injection-related and generalised type adverse events. Injection site pain, swelling, headaches and bruising are commonly encountered. These reactions range from 1:10 to 1:100 patients. Specific muscle weakness is related to spread or inaccurate injections affecting specific muscles and will be discussed as site-specific injection-related complications.

The "owl" appearance (Fig. 1) is a common problem encountered when the glabellar lines are treated. This mostly occurs due to the medial corrugator injection being placed too high. This decreases the activity of the medial frontalis, causing a medial eyelid droop and compensatory lateral frontalis hyperactivity. Appropriately placed injection directly into the medial corrugator will ensure that this does not occur. If observed, further low doses of botulinum toxin into the lateral frontalis will "drop" the lateral elevation.

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Figure 1: "Owl" appearance

Figure 2: Eyelid droop and lateral frontalis weakness (right)

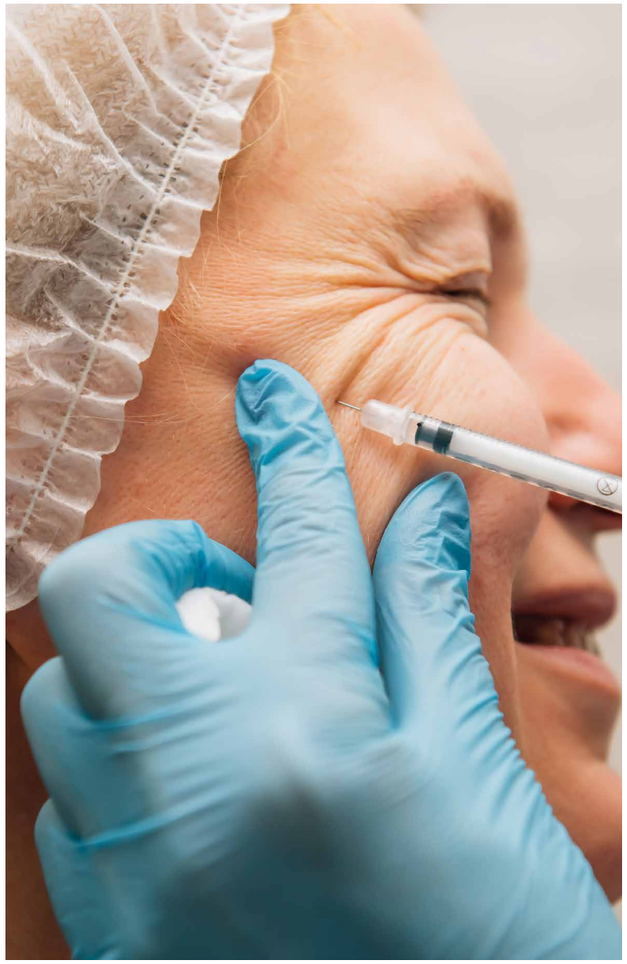
Figure 3 Left Zygomaticus Major weakness – asymmetric smile

Other muscle weakness affects the eyelid producing eyelid ptosis and or brow ptosis (Fig. 2); these are caused by either weakness of the levator palpebrae superioris (LPS) or lateral frontalis weakness. Spread or inaccurate injections into this area are the main causes of these observed weaknesses. Injections into the lateral corrugator should be placed superficially so as not to spread deeper through the orbital septum and weaken the LPS. Treatment of eyelid ptosis is mostly supportive; Iopidine® (Apraclonidine hydrochloride) 5mg/ml provides a short-lived (2-3mm improvement of ptosis). There are specific drug-related issues such as effects on intraocular pressure and corneal ulceration,[3] these need to be addressed, and it is best to prescribe this after discussion and examination by an ophthalmologist.

With lateral periorbital injections (crow's feet), specific muscle weakness produces an asymmetrical smile and on the extraocular muscles. An asymmetrical smile is often observed because the lower lateral canthal injection is too low (>1cm below the lateral canthal line). In this case, the toxin spreads to affect the superior attachment of the zygomaticus major (ZM) muscle- this results in a weakness of the muscles ability to pull on the modiolus and consequently, a drop of the lateral corner of the mouth results in an asymmetric smile (Fig 3). Treatment is supportive. Occasionally it is possible to inject the opposite ZM to balance the smile. This has to be done with care as it may not always balance the area.

The extraocular muscles may also be affected, resulting in diplopia. This may occur when either the lateral canthal lines or medial corrugator are inadvertently injected too deep and close to the orbital rim, spreading the toxin to the medial or lateral rectus muscle, respectively. Specialist ophthalmological opinion is required to manage this type of problem.

The most common weakness encountered is during treatment of the forehead upper facial lines; eyebrow ptosis (occurring in about 1:10 cases) and eyelid ptosis



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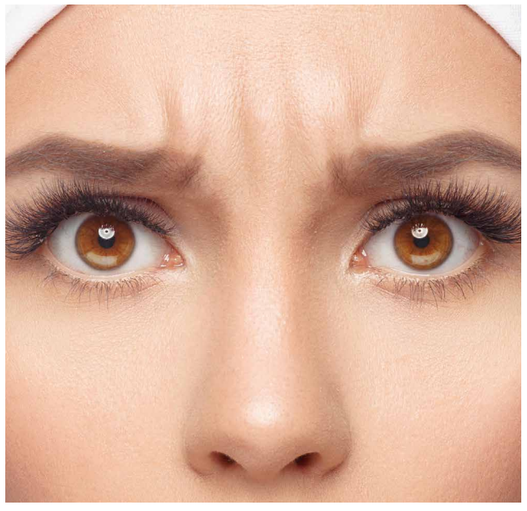


(1:100 cases). Brow ptosis is often caused by injection into the frontalis lower than the line of convergence of the frontalis[4]. In order to avoid this, it is important to assess the patient's individual anatomy and avoid injections too low. Some older patients rely on the lower part of the frontalis to keep their ageing ptotic brows elevated. In these cases, treatment of the forehead lines will also lead to the occurrence of brow ptosis due to the "hidden" brow ptosis being revealed.

Late effects: These are related to later immunological effects. Of particular importance is that of non-responders. This is postulated to be due to the formation of neutralising antibodies (up to 2.5%5). This is a diagnostic of true non-responders. In these very rare cases, immunological assessment for the presence of these antibodies will establish the diagnosis. If positive, the patient will require an "immunological rest" with a toxin-free period of three to six months. Following this, it may be appropriate to treat with a low immunogenic toxin, i.e. Incobotulinum toxin[6].

The most common non-response observed is a biological effect due to intra-patient variability of response to the toxin. In these situations, "top-ups" can provide additional toxin doses to treat the area.

Distant effects: These are very non-specific, non-toxic related effects, including flu-like symptoms, soft tissue swelling, breathlessness and swallowing difficulties, which are recognised post-marketing problems that have been reported. Often these are picked up through the various reporting mechanisms that medical practitioners should use when complications are encountered.

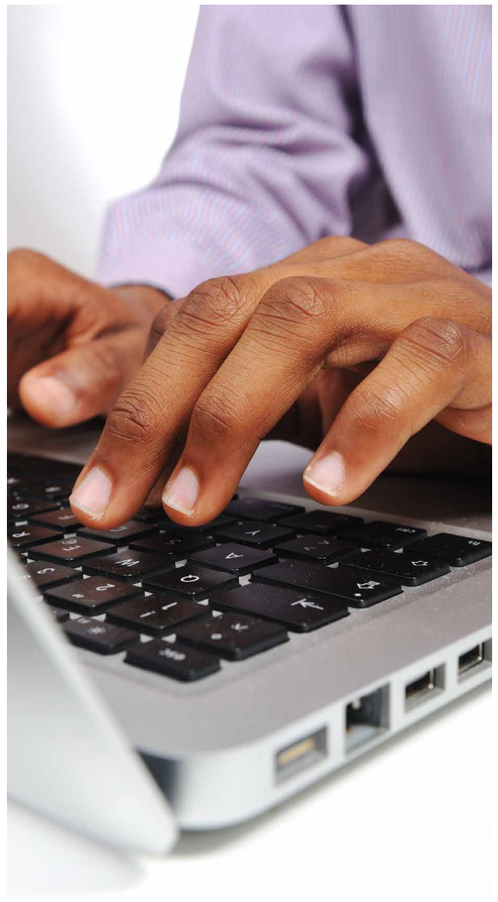
RECORDING AND REPORTING

In keeping with good medical practice, it is imperative that the consent process is adequately followed with full information given and consent forms signed as required for on-label and off-label treatments. Medical records of the patient with examination and recording of the static and dynamic appearance of the wrinkle lines. This may be recorded with validated scales or using photographs or, ideally, videos to record the dynamic and asymmetric movements. If and when a complication occurs, this should be fully recorded in the medical notes, and the appropriate treatment and supportive care is given to patients.

All pharmaceutical companies that market botulinum toxin in the UK have a Medical Affairs Department, which should be contacted and informed of the observed complication. They can also provide access to information on the management of the complication. As a medical practitioner in the UK, it is also in keeping with good medical practice and the "medical model" that the complication is reported directly to the MHRA via the "Yellow Card Scheme" [7]. This is an anonymous reporting scheme that will enable accurate post-marketing complications to be monitored and reported.

SUMMARY

Complications following botulinum toxins are fortunately rare, and seldom are they serious. Most can be prevented by a thorough knowledge of anatomy, appropriate injection technique and placement of accurate volumes in the appropriate anatomical position. Recognition and treatment of the complications that arise, with the required recording and reporting, will reduce the incidence and provide accurate surveillance of these adverse events while fulfilling medical practitioners requirements of good medical practice.



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